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Registries of Congenital Anomalies: EUROCAT

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Congenital anomalies are one of the potential adverse effects of the environment on reproductive health. Registries of congenital anomalies are useful to detect abnormal frequencies, clusters, and trends. Such registries should meet a number of conditions, including an appropriate population denominator, an efficient system for collecting information, standardized diagnostic procedures, postmortem examinations of stillbirths, and linkage of records. The EUROCAT (European Registration of Congenital Anomalies and Twins) program is a Concerted Action of the Commission of the European Communities initiated in 1979. One of its objectives is the surveillance of congenital anomalies as related to environmental hazards. This surveillance system covers at present 350,000 births per year in 15 countries. A number of problems encountered in the development of EUROCAT and in the course of ongoing activities are reviewed: populations coverage, classification of malformations, coding, definition and coverage of late fetal death, registration of induced abortion, validation of diagnostic information, registration of late diagnosed cases, and maintenance of motivation in data collection. The issue of confidentiality and the need for strict safeguards for the protection of individual privacy are emphasized.

Introduction

The diversity of reproductive health outcomes must be met by a diversity of information systems that respond in their design to the particular problems of definition and diagnosis of each outcome and its social and medical context. Here we concentrate on congenital anomalies.

There are many environmental factors that at one time or another have been suspected of playing a role in the causation of congenital anomalies. Chemical pollutants, dietary imbalance, ionizing radiation, pharmaceutical substances, and infections are, among others, known or suspected agents.

These same teratogenic agents may lead to other adverse pregnancy outcomes also. Congenital anomalies are monitored not only for their intrinsic importance as an important cause of morbidity and mortality, but for their use as an indicator of other potential adverse outcomes which may be less amenable to surveillance. Spontaneous abortions, for example, are not systematically reported, and later behavioral outcomes are as yet ill defined and unreliably recorded.

As potential indicators to monitor the effects of the environment on reproductive health, congenital anomalies have the relative advantage of often, though certainly not always, manifesting themselves within a few months of exposure.

Surveillance of the occurrence of malformed fetuses and children should indicate quickly a change in frequency and allow epidemiological investigation of the origin of the increase. Practically, the efficacy of surveillance may be limited by the quality of the information system and the lack of clear hypotheses underpinning statistical analyses.

Registries may be defined as information systems that exhaustively and continuously collect and record all the cases of a given disease in a well defined population. They address problems that cannot be appropriately studied by ad hoc surveys and for which selective hospital statistics or mortality data provide a biased picture.

Registries are useful for monitoring temporal or geographical differences in the frequencies of diseases, for specific epidemiological studies to identify etiological factors, to delineate vulnerable population groups, to study survival, or to plan and evaluate health care. The two areas of environmental monitoring and health service planning and evaluation are complementary, and the information collected should be appropriate to both.

A registry for congenital anomalies should meet the following criteria: *a*) a birth notification system must provide a population denominator and some minimal demographic information (maternal age, geographic distribution of residence); *b*) quality of the diagnostic information collected should be high and should be based on standard definitions and terminology; *c*) multiple sources of information should

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be used; *d*) linkage between different sources of information concerning the same child must be possible; *e*) case identification should be as minimally biased as possible by survival characteristics (stillbirths, neonatal deaths, induced abortions following prenatal diagnosis, and surviving livebirths should be equally reported) or by age at diagnosis, *f*) the analysis, validation, and follow-up of the data collected should be foreseen, either as part of the registry activities or by a closely collaborating institution, with the necessary facilities for processing statistics and with an interdisciplinary approach including clinicians, dysmorphologists, epidemiologists, and toxicologists/teratologists.

At the present, a number of registries for congenital anomalies exist in Europe. Registration may take the form of a national system of specific notification of congenital anomalies (England and Wales, Finland, Sweden, Czechoslovakia, and Hungary), of centralized birth notifications (Norway, Belgium, and Sweden), or of neonatal discharge records (Scotland), or specialized (often regional) registries using multiple sources of information. EUROCAT is a network of specialized regional registries in Europe with central coordination. Many of the larger European registries have been collaborating with other registries worldwide under the umbrella of the International Clearinghouse for Birth Defect Monitoring Systems. This paper will be restricted to our experience in EUROCAT.

EUROCAT is a concerted action of the Commission of the European Communities. The EUROCAT system of surveillance of congenital anomalies began in 1979 with a number of objectives: to provide baseline epidemiologic information on congenital anomalies in Europe, to monitor trends in frequency, and to assure the continuous evaluation of the population impact of prenatal diagnosis and termination of pregnancy and programs of primary prevention. It was to act as an information system that could respond quickly to specific needs, such as the assessment of the impact of environmental accidents or change or the suspicion of teratogenic influences from food, drugs, or other exposures. It was to establish a well-validated and documented case-series as a basis for etiologic, clinical, or health service research. Finally, it was to act as a catalyst for the setting up of information systems throughout Europe and ensure that these systems would collect comparable, standardized data. It was recognized that as congenital anomalies are relatively rare and good quality exhaustive data is expensive and difficult to collect, a standard European system could potentially allow countries to pool their data for studies and to exploit their differences by comparing these data. In 1990, 25 regional registries in 15 European countries (the twelve countries of the European Community, Malta, Switzerland, and Yugoslavia) covered approximately 350,000 births.

The EUROCAT registries were set up according to a number of general principles (*1*). They were to be population based, i.e., the population would be defined according to the residence of the mother in order to avoid biases due to hospital selection. They were to cover congenital malformations in livebirths, stillbirths, and induced abortions following prenatal diagnosis. They were to use multiple sources of information and active case-finding, in order to achieve more complete case ascertainment and more accurate case description than could be possible in systems dependent entirely on voluntary notification of cases. They were to extend registration to cases diagnosed after the neonatal period in order to collect valid information for the many late-manifesting congenital anomalies, most notably cardiac anomalies. Finally, they were all to report the same core information using the same coding system.

The method of data collection needed in order to follow these principles differed in the different regions of Europe according to local characteristics and constraints, such as the types of information systems already in place for covering the population of interest, the types of medical services available in each area and their utilization, and the availability of diagnostic information to the registry. The major issues in setting up the EUROCAT network are reviewed.

Definition of the Population

A registry can cover a population defined by the residence of the mother (population based) or by the place of birth (hospital based). What is important is often not the definition but the result obtained in terms of possible selection bias and quality of information.

It is assumed that the population of interest should be geographically defined because this can be most readily related to risk factors and to administrative information and population statistics. If the women resident within the geographic area who choose to deliver outside it (or are referred to outside hospitals) differ according to some risk factor for congenital anomaly from the resident women who choose to deliver within the geographic area, then there is selection bias in a hospital-based system but not in a population-based system.

A hospital-based registry may under certain conditions collect information that is not affected by selection bias. If all hospitals within a large geographic area are covered, then it may be only near the boundaries of the area that significant numbers of nonresident births are included, and most births to residents will take place within the area. Even where there are large numbers of immigrant and emigrant births, if it can be shown that the reason for immigration or emigration is not related to risk of congenital anomaly, then no selection bias should be present. It should be possible for a hospital-based system to trace *in utero* transfers (after prenatal diagnosis of malformation) entering or leaving the study hospitals for delivery and take these into consideration.

A hospital-based system can, however, have particular advantages for the collection of good quality information, since it can be easier to set up close collaboration with a limited number of clinicians and centers than to trace all deliveries to residents taking place in widely dispersed maternity units. This depends on the system of referrals and the cross boundary flow existing in the region. A hospital-based system may also have a more quickly available set of birth statistics when population statistics based on residence are compiled with a long delay, or when the

boundaries of the registry area do not coincide with the boundaries of a suitable administrative district.

A more difficult question is whether the populations covered can be considered representative of Europe. Since EUROCAT has a number of different objectives, and the geographic distributions of the many known and unknown risk factors may all be very different, it is impossible for a sample population to be always representative. Whether the results can be extrapolated to the entire European population must be judged for each individual analysis.

There is a conflict when collecting data for environmental studies, between the need to limit the size of the registry in order to collect complete and accurate data and the need to obtain coverage across extensive geographical areas in order to allow geographical comparisons and ensure that all localized risks will have available local health outcome information. Where a national birth defect monitoring system is in place, small specialized registries may be useful in addition to assess, on detection of a cluster, the possible role of incomplete ascertainment or to provide background epidemiological data needed to interpret the cluster and suggest hypotheses for investigation. Some specialized regional registries can serve to calibrate the national system, but this is not an easy objective to achieve, since reporting to the national system and to the specialized registry will not usually be independent.

At present, large geographic areas in Europe have no information system covering congenital anomalies, and it is not clear that putting resources into more complete geographical coverage rather than increasing data quality in representative regions would be advisable, keeping in mind also that environmental studies are only one of the uses of a congenital anomaly information system.

Definition and Coding of Diagnoses

All participating registries use the common nomenclature and code system of the British Paediatric Association Classification of Diseases (*2*), which is a five-digit extension of the ninth revision of the International Classification of Diseases. The McKusick Classification (*3*) is used for conditions with Mendelian inheritance. Up to eight congenital anomalies may be coded for each baby, and a syndrome, if recognized, can be coded. Cases are reviewed at the EUROCAT Central Registry by a pediatrician specializing in pathology and genetics, particularly with respect to the reporting and recognition of syndromes in babies with multiple anomalies.

There is a limited list of minor anomalies that are to be excluded unless occurring in combination with other major anomalies. Minor anomalies may not be unimportant in relation to environmental effects, but there is as yet little standardization in their recognition and they are probably more appropriately covered by other types of information systems than registries.

Coverage of Fetal Deaths

Early fetal deaths or spontaneous abortions are not at present covered by information systems, although they may be of great interest for the study of congenital malformations. Not all such fetal deaths will be known to hospitals or examined for malformation, and no population statistics for the number of spontaneous abortions occurring in the population are currently known.

Civil registration of late fetal deaths, stillbirths, is a requirement in all countries of Europe. Whereas formerly the most common limit distinguishing a spontaneous abortion from a stillbirth was 28 weeks gestation, this limit has been lowered in many countries in response to developments in neonatal care which have improved the viability of babies born at earlier gestational ages. The World Health Organization (WHO) recommended definition is 500 g (*4*), the average weight of a fetus of 22 weeks. EUROCAT registries aim to cover all fetal deaths from 20 weeks of gestation. This low limit eliminates any artificial distinction between livebirths and stillbirths of low gestational age. This is especially important for malformed babies considered not to be viable, such as those with anencephaly, since whether they are considered liveborn or stillborn may be influenced by medical customs or social or welfare considerations. In the case of malformed fetuses, a gestational age limit is preferable to a birth weight limit because malformed fetuses are often of lower birth weight than normal fetuses of equal maturity.

Some registries may have difficulties in obtaining information on fetal deaths not officially considered stillbirths, for example, those of 20–27 weeks of gestation. These fetal deaths of low gestational age will also not be found in birth statistics, leading to a slight discrepancy between numerator and denominator in calculations of prevalence rates. However, since malformations are selectively found in births of low gestation and since it is among malformed births that the distinction between livebirths and fetal deaths may be weakest, it is usually better to include malformed fetal deaths of low gestation in the surveillance system while remaining aware of the problems.

Some stillbirths or late fetal deaths may have obvious external malformations, while others may be found to be malformed only after pathological examination. A registry depends on there being a high autopsy rate and specialized fetal pathologists carrying out the autopsy for full information about stillbirths, and on the availability of autopsy records to the registry.

Registration of Induced Abortions after Prenatal Diagnosis

Prenatal diagnosis of malformation is becoming increasingly common in many European countries. For some malformations, this can be followed by termination of pregnancy or induced abortion. Laws regarding induced abortion differ between countries. It is not legal in Ireland or Malta. It is legal in many countries only up to the gestational age that defines a stillbirth, but exceptions may be made for malformed fetuses with conditions not compatible with life, e.g., anencephaly. In France, there is no upper gestational age limit for induced abortions.

Because the rate of prenatal diagnosis varies in time and between different geographic populations, it is essential

for the detection of changes and differences in the risk of many congenital anomalies that induced abortions should be registered and included in the calculation of prevalence rates. For the evaluation of the impact of prenatal diagnostic services, it is also necessary to have these cases registered. Unfortunately, this information proves to be difficult to collect in some areas. For some anomalies such as anencephaly, which is relatively easy to detect with routine ultrasound, the information problem is worsening as more and more clinics become involved, instead of the centralization of the diagnosis in specialized centers.

Induced abortions can be a special problem for hospital-based centers when women resident within the area are selectively referred to hospitals outside the area for prenatal diagnosis and induced abortion or, conversely, when nonresident women are selectively referred within the area. It may also be difficult for population-based centers to trace women leaving the area for prenatal diagnosis and abortion.

The only induced abortions covered by malformation registries are those that are carried out for fetal malformation. The majority of these fetuses would have resulted in live or stillbirth but for the early diagnosis. It is important to realize that induced abortions carried out for reasons other than malformation are not registered, whether the fetus is normal or malformed. In these cases, the fetus is usually not examined for malformation, and even if it is examined, it cannot be included in the numerator of prevalence rates when the total number of induced abortions carried out in the population is not included in the denominator. This denominator problem does not arise for induced abortions carried out because of fetal malformation, since they form at present a negligible proportion of the total births occurring in the population.

Precision of Diagnostic Information

Once an infant/fetus is known to be malformed, considerable attention must be given to obtaining precise diagnostic information. This can come from autopsy records, laboratory reports and cytogenetic analyses, medical genetics records, and records of specialized departments for treatment of the condition, including radiographs. The diagnosis may change or become more specific as further investigation is performed and this requires follow-up of the child during childhood through its medical records. Whether follow-up is needed, and what additional type of information should be sought, depends on the type of anomaly. Diagnostic precision involves two steps: are the investigations carried out and are the results of the investigations available to the registry?

Registration of Late-Diagnosed Cases

Many congenital anomalies are not yet diagnosed at birth or in the neonatal period, particularly certain cardiac anomalies, internal urogenital system anomalies, and central nervous system anomalies. Whether anomalies are diagnosed prenatally or in the neonatal period may depend on screening practices. For comparative purposes and to estimate the true prevalence rates of these conditions, sources of information extending beyond the neonatal period are necessary. Often these are the same sources of information which will allow follow-up of cases initially detected neonatally for further details on diagnosis.

Conflict between Quality, Quantity, and Rapidity

There is always a conflict between quality, quantity, and rapidity. The EUROCAT questionnaire is a compromise between quality and quantity. In general, it is difficult to collect data about risk factors without specifying the hypothesis in advance. The emphasis is therefore placed on the precision of the diagnostic information, while the variables concerning risk factors serve mainly as indicators of exposure, markers of cases requiring further search of the medical records or maternal interview.

The rapidity of data collection is in conflict with both the quality and quantity of data to be collected. It is clear that if our purpose is to detect a new thalidomide, this should be done as rapidly as possible. It is not necessary for the data to be absolutely complete or accurate. To facilitate rapidity, transmission to the central EUROCAT registry of incomplete case data, which can be updated when further information becomes available, is accepted. However, EUROCAT has not really been able to resolve this conflict, and up to now rapid analyses have been done on a local level but not on an international level. The international aspect of the project is more important for facilitating the communication between registries, so that local observations can be further investigated in other populations within a short delay and with known standard methods.

Active Data Collection and Motivation

Reliance on special or voluntary notification from clinicians or other health professionals is more suited to short, intensive ad hoc studies or to the registration of a limited list of very rare conditions. Routine registration of the full range of congenital anomalies requires the active consultation of medical records as well as setting up close contacts with clinicians. In a long-term registration system, one of the major problems is to maintain a good level of motivation for case finding. Various forms of feedback may increase motivation, including sending letters with information on available services to the practicing physicians, organizing seminars, distributing newsletters and reports with results from the registry, running a teratogen or genetic information service in parallel to registration activities, and even supplying items of mutual benefit such as books, journals, computers, or cameras. It is important that the data collected are seen to be of immediate use and of local relevance. This favors regional rather than national registries and the employment of personnel who can use and evaluate the data as it is being collected.

Confidentiality

Confidentiality is a major issue for epidemiological registries. Registries used for any type of disease or provision

of health services raise the issue of confidentiality and protection of individual privacy. Strict safeguards must be established to prevent unauthorized use of the records.

In most but not all of the EC countries, special codes have been enacted for the use of personal data for research, which apply to health data. In each country, the EUROCAT registries are bound to respect the local regulation regarding medical databases. In addition, European countries adhere in principle to the general principles recommended by the Assembly of the European Science Foundation in a 1980 statement concerning the protection of privacy. Special regulations apply also in some countries to the transmitting of computerized information across international borders.

From the beginnings of EUROCAT, it was agreed that the Central Registry will receive no information that would enable anyone to identify directly or indirectly the malformed baby or its parents. Names and addresses of cases and hospitals are never sent to the Central Registry. A local serial number only is transmitted for each baby, which is used in correspondence with the local register, or when there is a need for additional information or further investigation. This rule is applied both for information reported on precoded forms or on magnetic tapes (*1*). Such a multilevel procedure with repeated safeguards for confidentiality prevent any unauthorized access to private data, and prevent a direct approach to the baby or its parents. EUROCAT has shown that a multinational use of epidemiological data for the purpose of environmental surveillance is feasible while respecting strict rules of confidentiality and protecting the privacy of the individual.

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